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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/717,057	11/21/2000	Michael Brines	10165-010-999	5119

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Pennie & Edmonds LLP
1155 Avenue of the Americas
New York City, NY 10036-2711

EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/717,057	BRINES ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-7 and 9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-7 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10 July 2006 has been entered.

Status of Application, Amendments and/or Claims

Applicant's arguments filed 10 July 2006 have been entered in full. Claims 2-7 and 9 are pending and under examination. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

The information disclosure statement(s)(IDS) filed 10 July 2006 was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

Claim Rejections - 35 U.S.C. § 112, First Paragraph, Scope of Enablement

Claims 2-7 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method of enhancing the function of normal, damaged or injured central nervous system tissue in a mammal, **wherein said damage or injury is caused by trauma, stroke or cerebral hypoxia-ischemia**, comprising administering peripherally to a mammal in need thereof a peripherally effective, non-toxic effective amount of recombinant erythropoietin for enhancing central nervous tissue function; (claim 2) so that the associative learning or memory in/of the mammal is enhanced; (claim 3) so that cognitive function is enhanced;

a method of enhancing the function of normal, damaged or injured excitable tissue in a mammal, comprising administering peripherally to a mammal in need thereof a peripherally effective non-toxic effective amount of recombinant erythropoietin for enhancing excitable tissue function, wherein said excitable tissue is **central nervous system tissue or sensory axonal tissue** (claim 4);

a method of enhancing the function of normal, damaged or injured excitable tissue in a mammal, **wherein said damage or injury is caused by sensory axonal degeneration, autoimmune encephalomyelitis, or myocardial infarction**, comprising administering peripherally to a mammal in need thereof a peripherally effective, non-toxic effective amount of recombinant erythropoietin for enhancing excitable tissue function (claims 5-7, 9);

does not reasonably provide enablement for the instant claims as recited.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

commensurate in scope with these claims. The basis for part of this rejection is set forth at pages 3-7 of the previous Office Action (09 January 2006).

Applicant addresses the 35 U.S.C. § 112, First Paragraph, Scope of Enablement according to each claim. For claims 2-3, Applicant states that the references of record (submitted in the previous Office Action, 09 January 2006) enabled the use of the current methods for damaged or injured tissue resulting from a variety of conditions: trauma, surgical trauma, cerebral hypoxia-ischemia and schizophrenia. The submitted references and arguments were not found to be persuasive for reasons already made of record (09 January 2006). Applicant discusses the Ehrenreich reference (submitted 09 January 2006). Applicant argues that the purpose of the Ehrenreich reference is to determine whether EPO satisfied certain pre-requisites that would create a basis for its use as an add-on strategy for the treatment of schizophrenia. Applicant discusses the data from the Ehrenreich reference. Applicant discusses Miu *et al.* and Juul (newly submitted references). Applicant contends that the various references have established that EPO can enhance the associative learning, memory or cognitive function related to numerous injuries resulting from trauma, such as blunt (Lu reference) or surgical trauma (Mogesen reference), toxins (Miu reference), hypoxia-ischemia (Kumral reference), schizophrenia and cognitive dysfunction or stroke (Ehrenreich reference).

Applicant's arguments have been fully considered but are not found persuasive. Firstly, some of the limitations discussed by Applicant are encompassed by the scope of enablement determined by the Examiner (i.e. enhanced function of normal, damaged/injured central nervous system tissue, wherein damage/injury is caused by

trauma, stroke, ischemia and wherein associative learning/memory/cognitive function is enhanced). The Juul and Miu *et al.* references would be applicable to damage, injury caused by trauma, stroke and/or ischemia. Juul teaches that EPO treatment decreases the structural damage resulting from experimental brain injury (*in vivo* studies, page 39). Miu *et al.* teach that one way hypoxia/ischemia can produce neuronal damage is through increased glutamate release associated with insufficient glutamate recovery. Miu *et al.* teach EPO protection against glutamate neurotoxicity in the amygdala (Discussion, page 226-page 227). The Ehrenreich reference is not applicable. Ehrenreich *et al.* teach that EPO crosses the blood-brain barrier and that there are more EPO receptors in the brain of schizophrenic patients. The reference does not teach a nexus between that and the treatment of schizophrenia. The reference fails to teach a human displaying schizophrenia, whose schizophrenia can be treated with peripherally administered EPO.

The scientific reasoning and evidence as a whole indicates that the instant claims are not enabled for the full scope of a method of enhancing the function of normal, damaged or injured central nervous system tissue (i.e. any type of damage/injury to the central nervous system) in a mammal, comprising administering peripherally to a mammal in need thereof a peripherally effective, non-toxic effective amount of recombinant erythropoietin for enhancing central nervous tissue function; (claim 2) so that the associative learning or memory in/of the mammal is enhanced; (claim 3) so that cognitive function is enhanced.

For claim 4, Applicant argues that Keswani teaches that systemic EPO enhances the function of peripheral nervous system tissue, sensory axons and Schwann cells subjected to peripheral neuropathies and other neurodegenerative diseases. Applicant argues that Keswani demonstrated to one of ordinary skill in the art that the peripheral administration of effective doses of EPO effectively enhanced the function of damaged excitable peripheral nervous system tissue.

Applicant's arguments have been fully considered and are found partly persuasive. Keswani *et al.* teach the use of EPO in dying-back axonopathies, characterized by degeneration of the most distal portions of axons. Keswani *et al.* state, "our data suggest that recombinant EPO may be therapeutically useful in peripheral neuropathies and other neurodegenerative diseases **where dying-back axonal degeneration is a characteristic feature**"(page 815-top of page 816). Keswani *et al.* examine the effect of EPO in an animal model of distal axonal degeneration. In the rat model, oral acrylamide administration to rats results in severe dying-back degeneration of sensory and motor fibers in the absence of significant neuronal death (page 821, last paragraph-page 822). Claim 4 recites enhancing the function of normal peripheral nervous system tissue, which the specification and art of record fail to teach. In addition, the instant claim encompasses any type of damaged/injured peripheral nervous system tissue. Keswani *et al.* teach that rats given EPO had significantly less **sensory axonal degeneration.** Claim 4 is not enabled for enhancing the function of normal peripheral nervous system tissue or enhancing the function of any type of damaged/injured peripheral nervous system tissue. However, claim 4 has now been scoped to recite,

"wherein said excitable tissue is central nervous system tissue or sensory axonal tissue".

The scientific reasoning and evidence as a whole indicates that claim 4 is not enabled for the full scope a method of enhancing the function of normal, damaged or injured excitable tissue in a mammal, comprising administering peripherally to a mammal in need thereof a peripherally effective non-toxic effective amount of recombinant erythropoietin for enhancing excitable tissue function, wherein said excitable tissue is peripheral nervous system tissue.

For claims 5-7 and 9, Applicant argues that the Examiner's assessment is overly restrictive given that in the Office Action, dated 05 April 2005, the Examiner indicated that the claims were enabled for stroke and autoimmune encephalomyelitis in addition to diabetic neuropathy. Applicant discusses the Keswani and Ehrenreich references.

Applicant's arguments have been fully considered and are found partly persuasive. Keswani *et al.* teach that dying-back axonal degeneration is a characteristic feature of diabetic sensorimotor polyneuropathy and HIV-associated sensory neuropathy and toxic neuropathies. Claim 5 has now been scoped to recite, "wherein said damage or injury is caused by sensory axonal degeneration, autoimmune encephalomyelitis, or myocardial infarction". Applicant discusses Ehrenreich, however, the Ehrenreich statement was based on citations from other references, which were not submitted with the instant application.

Lastly, Applicant directs the Examiner's attention to newly submitted references Strum *et al.* and Erbayraktar *et al.* Applicant discusses the data of Strum and

Erbayraktar. Applicant states that Strum demonstrates EPO's ability to enhance frataxin expression in normal and injured/diseased cells. Applicant states that Erbayraktar demonstrates that the systemic administration of CEPO enhances motor functioning excitable tissue injured or damaged due to radiation, and one of ordinary skill in the art would expect that erythropoietin would also enhance the function of excitable tissues in this indication.

Applicant's arguments have been fully considered but are not found persuasive. The Strum reference is not applicable to the broad scope of enhancing the function of damaged/injured excitable tissue in a mammal. Excitable tissue includes the peripheral nervous system. Strum *et al.* teach an increase of frataxin expression in lymphocytes obtained from dialysis patients 48 hours after receiving EPO compared with lymphocytes obtained from the same patients before EPO administration. Strum *et al.* **do not teach** decreased ataxia, dysarthria, diabetes mellitus or hypertrophic cardiomyopathy (symptoms of Friedreich's ataxia) upon EPO administration in patients. The other experiments of Strum were employed in tissue culture. The *in vitro* experimental data presented is clearly not drawn to subjects suffering from Friedreich's ataxia. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, pg. 4) teaches that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous

and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In vitro*).

Erbayraktar *et al.* discuss gamma knife radiosurgery for the treatment of brain tumors. Radiation-induced brain injury leads to necrosis of the surrounding normal brain tissue. Erbayraktar *et al.* teach that the presence of a structural lesion may further predispose surrounding tissue to injury by physical distortion, inflammation and the development of fibrosis. Erbayraktar *et al.* teach improvement of motor function upon CEPO administration. However, the Erbayraktar *et al.* reference is not applicable the full scope of enhancing the function of damaged/injured excitable tissue in a mammal. The damaged/injured peripheral tissue was due to a specific type of brain injury (radiation-induced brain injury). It is unpredictable whether EPO could be used to treat spinal injuries or other types of paralysis (i.e. damaged/injured peripheral tissue caused by different types of injury). Secondly, Erbayraktar *et al.* teach the administration of EPO **prior to the radiosurgery** and one daily for 10 days for following the surgery to minimize collateral necrotic tissue damage. The instant claims do not read on administering EPO before injury. **Most importantly, Erbayraktar *et al.* teach that the *hematopoietic activity of EPO is undesirable* in this setting, increasing erythrocyte number and predisposing to thrombosis.** Erbayraktar *et al.* state, "to avoid these potential adverse effects, **we developed carbamylated EPO (CEPO)**

which does not stimulate bone marrow" (abstract). The instant claims recite the use of EPO.

The scientific reasoning and evidence as a whole indicates that claims 5-7 and 9 are not enabled for the full scope of a method of enhancing the function of normal, damaged or injured excitable tissue in a mammal, comprising administering peripherally to a mammal in need thereof a peripherally effective, non-toxic effective amount of recombinant erythropoietin for enhancing excitable tissue function.

NEW REJECTIONS/OBJECTIONS

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 2-7 and 9 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 28-31, 33-37, 39, 52, 55, 57-59 of copending Application No. 09/547,220.

The claims of copending Application No. 09/547,220 differ from the claims of the instant application in that Application No. 09/547,220 teach a method for treating cerebral ischemia in a mammal comprising administering peripherally EPO to a mammal. However, it is noted that the instant claims are drawn to enhancing the function of normal, damaged or injured central nervous system or excitable tissue in a mammal comprising administering peripherally EPO to a mammal. Damage or injured central nervous system and/or excitable tissue would include tissue found in cerebral ischemia. Thus, although the conflicting claims of copending Application No. 09/547,220 and the instant application are not identical, they are not patentably distinct from each other. It would have been obvious to modify the methods of the instant claims to include treating cerebral ischemia. One having ordinary skill in the art would have been motivated to make such modifications because the instant specification teaches that EPO can be used to treat damaged central nervous tissue caused by ischemia. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

35 U.S.C. § 112, First Paragraph, Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 5 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification and the art of record fail to teach that EPO can cross the blood/brain in routes besides intravenously and intracranially. The specification and art of record fail to teach/demonstrate that EPO can cross the blood/brain barrier via different routes of administration (e.g. oral, topical, intraluminal, inhalation, parenteral) and enhance the function of normal, damaged, injured central nervous system tissue or excitable tissue in a mammal. Parenteral administration would not only include intravenous but also subcutaneous and intramuscular administration.

Due to the large quantity of experimentation necessary to demonstrate that EPO can cross the blood/brain barrier via oral, topical, intraluminal, inhalation, subcutaneous and/or intramuscular administration and enhance the function of normal, damaged, injured central nervous system tissue or excitable tissue in a mammal, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, and the breadth of the claims which fail to recite any parameters regarding routes of EPO administration, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RMD
09/13/06

MARIANNE P. ALLEN
PRIMARY EXAMINER
AU1647

9/21/06